Tuberculosis (TB), despite the anti-mycobacterial therapies and vaccine, is a deadly infectious disease with about 12 million incidents worldwide. Existing Bacillus Calmette-Guerin (BCG) vaccine is unquestionably inexpensive, safe and effective against severe forms of childhood TB but appears to be limited effective against adult pulmonary disease in endemic areas. Genetic variation in population is the major obstruction inhibiting validation of biomarkers for protective human immunity against TB. Since, current TB cases are presenting new challenges with threats of HIV co-infection therefore various attempts are being done to develop a new modified vaccine against it at global platform.

Tuberculosis (TB), despite the anti-mycobacterial therapies and a widely accepted BCG vaccine are existing and unquestionably working effectively with apparent reach to common man. BCG vaccine regimen is satisfactorily protecting to infants from natural mycobacterial infection with good efficacy but is reported suspicious in adults who have already been exposed to environmental mycobacterium and developed immunity against it as memory response. Surprisingly, the BCG ability was noticed getting impaired by this developed immunity in said adults. Nevertheless, putting it at health priority; efforts are regularly being made by global scientists to update the existing form of BCG so that it can efficiently manage the infections in adults also.

Why BCG is unsuccessful in adults?

Several hypothesis has been postulated to explain the failure of BCG, including geographic climate, latitude, host genetic background and major strain used in BCG vaccine. Including them, some major reasons of BCG failure are:

- Genetic variation in BCG strains
- Genetic variation in populations
- Interference by environmental mycobacterium (usually non-BCG)
- Interference by concurrent parasitic infection
- Resistance of M. tuberculosis against BCG effects in already infected individuals

Efforts made to overcome the failure

Though, various efforts have been done and few are still continued to modify the existing BCG vaccine to circumvent its ambiguity but few of them, got healthy attention are discussed below.

Modified Vaccinia Ankara Virus (MVA) vectored vaccine

MVA vaccines have been found to be immunogenic and protective against various infectious agents including immunodeficiency viruses, influenza, measles virus, tuberculosis, Plasmodium parasites and smallpox etc. In TB, Modified Vaccinia Ankara-expressing Ag85A, a protein involved in mycobacterial cell wall synthesis is used as a new TB vaccine aimed at enhancing immunity induced by BCG. The vaccine was reported well tolerated with insignificant serious adverse events. It induces potent and durable T-cell responses through adequate expression of IFN-gamma, TNF-alpha, IL-2, IL-17 and GM-CSF. Interestingly, the induction of novel TCR, T-cell populations that have not been previously described in humans was similarly observed in children and adolescent both.

Subunit vaccine (2nd generation vaccine)

In this, several antigens viz. Esat-6, CFP10, which are encoded by RD1 (region of deletion 1) that is missing in BCG, Ag85A/B, MPT63,64,83 etc. together with some cell bound antigen like Mtb39A are given as subunit vaccine to immunize TH1 cells against M. tuberculosis antigens which are secreted in early steps of infection. As a result, more rapid and effective mobilization of T-cells occur at the site bacterial multiplication which further suspend the infection and reduce the risk of active TB.

Adjuvant based BCG (3rd generation vaccine)

In these approaches the antigenic protein and specific cytokine’s expression is added to increase the vaccine efficacy. One such adjuvant based vaccine, MVA/IL15/Smbt, over express the five mycobacterium tuberculosis antigens, Ag85A, ESA76, HSP60, and Mtb 39 and molecular adjuvant IL-15 which as a result elevate the level of protection in human body. Interestingly, the level of protection remain unchanged after 4 months of introduction, while protective responses induced by BCG get decrease during this time.

Recombinant (rBCG) vaccine

In this approach, the efficiency of BCG is tried to enhance through insertion of selected genes such as Esat-6 and CFP-10 encoded by RD1 region which was deleted during attenuation of BCG. Since, these are immunodominant antigens able to induce immunostimulatory cytokines therefore, rBCG can elicit higher INF-Y production than BCG, which is a typical character of T1 type immune response. Moreover, strategies are also developed to make BCG easily digestible by host dendritic cells so that it could readily be processed and presented on cell surface of them to induce T-cell immune response. Likewise, a rBCG strain (rBCGΔureCΔγ) was prepared with ability to secrete listerotlysin (Hly), a cytolsin of Listeria monocytogenes (forms pores in phagosome membrane) and to block early acidification of phagosome. As a result, RBCGΔureCΔγ can translocate to the cytoplasm of infected dendritic cells, where antigen can readily be presented on cell surface through cytosolic pathway of antigen processing and presentation.

Since, there is crucial requirement of cellular immune response to control the mycobacterium infection therefore, BCG is genetically engineering in such a way where it could elicit not only an optimum level of INF-Y secretion, but also the humoral response.

Polyvalent DNA vaccine

Genetic immunization is attempted by this category of vaccine. Since, the purification and production of this type of vaccine is generally less expensive with nearly same or better results therefore, used as model to test the immunogenicity and protective activity of single M. tuberculosis antigen. The immunogenic protein antigens mainly tested under these approaches are Esat-6, MPT64, Ag85A/B and MPT83. Altogether, they have introduced the level of cell mediated immune response with broader T cell repertoire than subunit vaccine. The use of DNA vaccine cocktail, the combination of two or more antigens have provided improved level of protection than monovalent DNA vaccine. Though, poor level of immunity induced by recombinant DNA vaccine has been shown which can inhibit Mycobacterium tuberculosis infection in animals.

In this step, a strategy may be constituted to immunize and boost an anti-mycobacterial immune response in adult subject already exposed to M. Tuberculosis and suffering with latent TB infection. This strategy may be used to specifically target the adult population of country where TB is endemic.

4. A vaccine targeting to mycobacterial antigens which are involved in bacilli dissemination to other organs such as lungs (major and usual site of TB development), may provide expected outcomes by interfering the dissemination. An HBHA-based vaccine may be an example for this immunization strategy.

Conclusions

New vaccines should be more powerful than BCG and safe enough for use in HIV endemic areas. These need to induce strong cellular and humoral immune response by enhanced production of IFN-Y both by CD4+ and CD8+ cells. Though, a hard dedicated work is need to do to solve the TB puzzle because hundreds of question are still unanswered. But any vaccine work better than BCG or shows “only” a 50% efficacy in adults may save millions of lives in economically poor and developing countries.

References


Stages in tuberculosis life cycle which may be considered as potential targets for vaccine

1. The transfection stage where M. tuberculosis initially infect to other neighboring cells, may be a better target to develop an effective vaccine.

2. An agent able to induce strong cell-mediated immune response against antigens which are actively secreted and expressed in the early stages of infection may induce rapid mobilization of T lymphocytes at infected site, which may further suppress bacterial replication and reduce the possibility of developing active TB disease.

3. A vaccine aimed at blocking first step infection by specific antibodies may always be a better option. Though, most of the licensed vaccines currently used in humans, work in this way but no experimental vaccine has ever been shown which can inhibit M. Tuberculosis infection in animals.

4. A vaccine targeting to mycobacterial antigens which are involved in bacilli dissemination to other organs such as lungs may be a better option. Though, most of the licensed vaccines currently used in humans, work in this way but no experimental vaccine has ever been shown which can inhibit M. Tuberculosis infection in animals.